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Blood Transfusion: Use and Abuse of Blood Components

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Transfusion of whole blood and some blood components may result in serious or fatal complications, among which hepatitis is most frequent (20,000 to 30,000 cases and 3,000 deaths a year). Although hepatitis B virus (HB Ag) sometimes is implicated in posttransfusion hepatitis, non-A non-B virus(es) (hepatitis "C" virus) probably accounts for most posttransfusion hepatitis.

Half of all blood transfusions may be unnecessary.

Responsible transfusion practice requires use of appropriate blood components for which there is adequate justification. Transfusion of red blood cells should be given as packed cells in most instances and whole blood should seldom be used.

TRANSFUSION THERAPY for anemia should be considered a "last resort" because of the many dangers to the recipient. There are few injectable agents used in medicine that carry so many and such severe hazards for a patient.

Several years ago it was estimated that nearly 3,000 deaths were occurring annually in the United States as a result of transfusion of 3.5 million patients.[1] The incidence of unnecessary transfusion was then estimated, as it is today, to be approximately 50 percent of all transfusions.[2] In today's courts of law, approximately 1,000 of those deaths might have been judged the result of involuntary manslaughter.[3] It has been recently estimated that more than 8 million units of blood and blood products are now being used in this country each year[4] with 20,000 to 30,000 cases of posttransfusion hepatitis and an annual death rate of 3,000 people from posttransfusion hepatitis alone.[5]

Complications of blood transfusion (Table 1) are of many types and some are extremely dangerous to the life of patients and, incidentally, to the security of physicians. Table 2 lists the types of transfusion reactions encountered.[10]

Hepatitis occurs with greater frequency (0.3 percent to 0.8 percent)[11] than the other serious complications. Hepatitis carries a mortality rate of approximately 1 percent to 20 percent[11] and, although hepatitis B virus (HB Ag) has been implicated in posttransfusion disease, most posttransfusion hepatitis is due to hepatitis "C" virus (non-A non-B hepatitis virus).[12] Hepatitis A disease is usually less severe than that resulting from hepatitis B virus and residual severe liver disease and death are infrequent.[13] Although there is a test for hepatitis A antibody in serum (immune adherence test),[14] there is no practical test for hepatitis A virus in blood products[13] and cur-

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ABBREVIATIONS USED IN TEXT
ACD = citric acid, trisodium citrate, dextrose
ATP = adenosine triphosphate
CPD = citrate phosphate dextrose
2,3-DPG = 2,3-diphosphoglycerate

rent tests cannot detect all donors capable of transmitting hepatitis B positive hepatitis.[15] Donor services, after excluding commercial and hepatitis antigen positive donors, report a frequency of hepatitis of 3.7 cases per 1,000 units transfused, indicating that it is not yet possible to identify all donor carriers. Donors with hepatitis B antibodies should not be excluded because they offer some protection against the disease.[15]

Of volunteer donors, 0.1 percent to 0.4 percent are hepatitis B antigen carriers but the rate is much higher among commercial donors; 5 percent of drug addicts are thought to be carriers and the normal person who is infected with hepatitis B antigen rarely becomes a carrier. If he or she does, it is probably for life.[14]

Recent advances in hepatitis research include successful transmission of hepatitis caused by hepatitis B, hepatitis A and hepatitis "C" viruses to nonhuman primates. Development of tests for antibody has led to improved immune serum globulin for prevention of infections. Preparation of hepatitis B inactivated vaccine now under trial offers hope for control of hepatitis B disease. The safety, immunogenicity and protective effect are yet to be proved. The new problem is the recent recognition of a non-A non-B variety of virus (hepatitis "C" virus) caused hepatitis in patients receiving multiple transfusions.[14] This virus (or group of viruses) probably accounts for most cases of posttransfusion hepatitis. So, with all that has been accomplished in research and test developments, there is no way to insure that any unit of whole blood is free of hepatitis virus.

We physicians have an obligation to keep current with developments in transfusion therapy in order that we utilize the safest and most effective blood component in treating patients.

TABLE 1.—*Complications of Blood Transfusion*

Transfusion Reactions
Hepatitis
Sensitization
Infections:
Brucellosis
Syphilis
Malaria
Trypanosomiasis[6]
Cytomegalic virus[7]
Epstein-Barr virus[8]
Air embolism
Thrombophlebitis
Disseminated intravascular coagulation
Dilution thrombocytopenia
Potassium and/or ammonium toxicity
Pharmaceutical incompatibility with drugs taken by donor
Graft vs host reaction (donor lymphocytes vs recipient)[9]

Modern Transfusion Therapy Means Component Therapy

Component therapy not only allows achievement of a more effective therapeutic level of the needed blood fraction but it extends the available blood resource since each unit of whole blood can meet the needs of multiple recipients. The proper use of blood requires:[4]

TABLE 2.—*Transfusion Reactions*

Cause	*Symptoms*	*Frequency*	*Prognosis*
Allergy	Itching, urticaria, fever, bronchospasm, angioneurotic edema	Common	Good
Unknown (febrile)	Chills, malaise, fever, headache	Common	Good
Circulatory overload	Dyspnea, cough, hemoptysis, tachycardia	Rare	Good
Contaminated blood	Chills, fever, headache, backache, delirium, hematemesis, diarrhea	Rare	Serious
Red cell incompatibility	Chills, fever, headache, backache, hematuria, oliguria, jaundice	Moderate	Serious
Antibodies			
1. RhD in gamma fraction	Same	Rare	Good (delay in transfusion)
2. Penicillin	Same	Unusual	Good
Sensitivity to donor:			
Leukocytes	Chills, fever, malaise, headache, confusion	Common	Good
Platelets	Same	Rare	Good
Plasma	Same	Rare	Good

- Knowledge of pathophysiology of condition being treated.
- Identification of the specific deficiency needed by the patient.
- Choice of appropriate component for therapy.

Multiple hazards to the patient and attendant risks to physicians and hospitals will be reduced by elimination of unnecessary blood transfusion and by proper use of blood component therapy when blood transfusion is necessary.

The indications for blood transfusion are relatively few; the usual being to maintain or increase blood volume and also to improve or maintain oxygen carrying capacity, with the unusual being to replace toxic circulating blood or to enhance coagulation, or both.

In most instances, use of whole blood for volume maintenance would be limited to considerable acute blood loss and would require two or more units. It has been observed that acute blood losses of 1,000 to 1,500 ml of blood from previously normal adults can be compensated by use of plasma expanders if blood loss can be stopped.[16] Spontaneous reestablishment of hemoglobin begins soon after an acute bleed in most cases, the amount increasing 0.1 to 0.3 gram per dl per day.[17] There are prevalent misconceptions that may account for some abuse of transfusions. Some surgeons have expressed the view that healing will be more rapid if hemoglobin levels are maintained within the normal range. We are aware of no convincing evidence to support this belief. Some surgeons and anesthesiologists believe that a long operation is in itself an indication for whole blood transfusion; that all patients with symptoms of shock and blood loss need whole blood, and that it is unsafe for mildly anemic patients to undergo a major operation without preoperative transfusion to elevate the hemoglobin level. Many also believe themselves able to estimate operative blood loss accurately. These misconceptions account for unnecessary transfusion and risks to recipients.

One series of 100 patients with benign ulcers underwent elective partial gastrectomy for reasons other than recent severe hemorrhage. In only two was blood transfusion required during operation and in none afterward.[18] Dr. Crosby has indicated that, if volume of blood is normal, a hemoglobin level of 7 grams per dl is sufficient for tissue oxygenation in most surgical situations.[19] One well known surgeon of this area has stated that a patient with a hemoglobin concentration of 11 grams per dl before operation would usually be safer in donating a pint of blood than in receiving one.[20]

The use of plasma substitutes for volume maintenance does not receive the attention it deserves. Patients requiring only one or two units of blood should probably receive a plasma substitute.[16] It is desirable to exclude the plasma from the transfusion unit if possible because leukocytes and platelets form microaggregates in the donor plasma and their concentration increases with storage time. These microaggregates may become trapped in the recipient's pulmonary microcirculation and promote respiratory failure. Donor leukocytes may also activate cellular and humoral immune response in the recipient resulting in sensitization of an existing or subsequent organ transplant.[21]

The use of blood to improve oxygen carrying capacity in an anemic patient is complicated by the requirement to assess the needs of the patient. These needs for oxygen vary depending upon altitude, age and physical activities. It is helpful for physicians to be acquainted with the "normal" or "usual" hemoglobin levels for the various ages and activities of male and female patients in their own geographical area. For example, we have observed the usual hemoglobin level for young housewives at sea level to be between 10.5 and 13.5 grams per dl. In young men of similar age the range is from 12.5 to 16 grams per dl. In 633 "normal" women in Spokane, Washington, (elevation 2,000 feet) a mean hemoglobin level of 12.55 grams per dl was reported.[22]

In considering transfusion of whole blood or red cells, it is important to recognize that each unit (pint) will increase the hemoglobin level by only 1 to 1.5 grams per dl.[17]

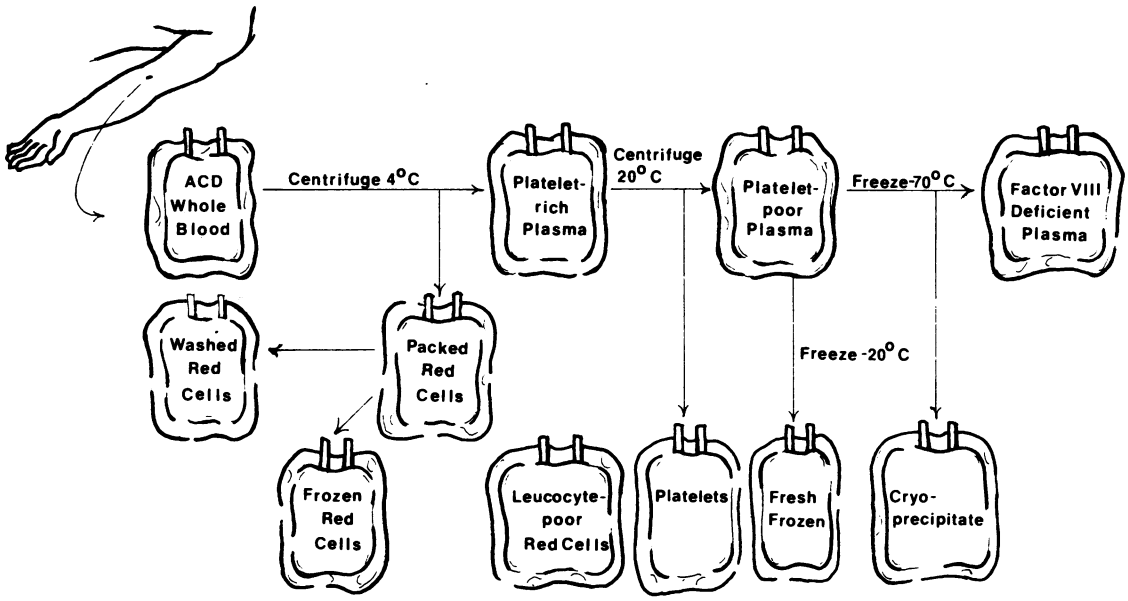
The merits of a single unit transfusion must be weighed against the many hazards to the recipient when he or she will have benefit of only a 5 percent to 10 percent increase in hemoglobin from the single unit.

Twelve years ago a review of this subject in a Southern California hospital showed that 47 percent of transfusions were single unit and that 80 percent of those were probably unnecessary. One year later, after several educational presentations on blood transfusion therapy, the single units had dropped to 42 percent of which 52 percent were probably unnecessary. In 1972 the single unit

transfusion rate was 21 percent, and 43 percent of these were deemed unnecessary. In 1974 single unit transfusions were 19 percent, and 30 percent of these were felt to have been unnecessary.[23]

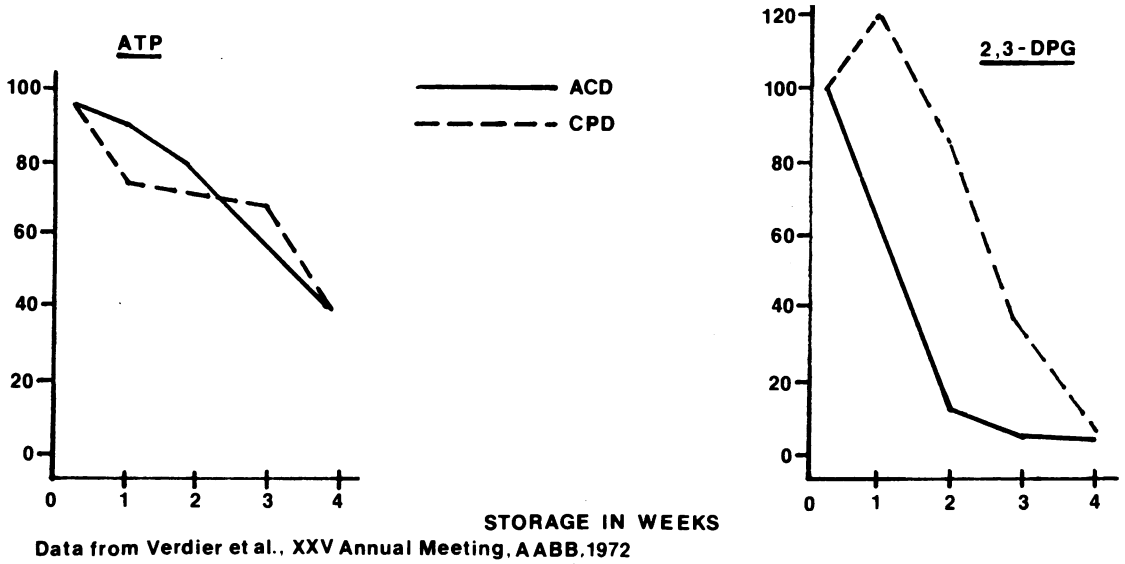
Improvements in transfusion practice are slow. Component therapy must be considered when we think of transfusion.

Most blood banks accept donors who have been screened by a physician who takes the blood pressure and pulse, and records the temperature. The patient must be of a certain age, and weight, and must have had a history of good health. (Criteria for donor selection are included in the Appendix.)



PRIMARY INDICATIONS	Anemia & Hypovolemia	Organ Transplants Patients	Anemia	Leucocyte Reactions	Thrombo-cytopenia	Multiple Factor Deficiency	Hemophilia A	Hemophilia B

Figure 1.—Scheme for component separation (Modified from Hinkes and Steffen[24])



Data from Verdier et al., XXV Annual Meeting, AABB, 1972

ACD = citric acid, trisodium citrate, dextrose
ATP = adenosine triphosphate
CPD = citrate phosphate dextrose
2, 3 DPG = 2, 3-diphosphoglycerate

Figure 2.—Effects of storage of whole blood in ACD and CPD solutions

The blood collected in citric acid, trisodium citrate, dextrose (ACD) solution may be processed for component therapy in a manner illustrated by Figure 1.[24]

Such separation as indicated in Figure 1 provides convenience, relatively low cost, and safety. When the blood is stored in the anticoagulant solution, erythrocytes will undergo chemical and physical changes which have been referred to as *storage lesion*.[25] They lose their capacity to deliver oxygen efficiently to the tissues and ultimately their capacity to survive for more than a few minutes in the circulation of the recipient. The rate at which the storage lesion occurs is a function of the preservative and condition of storage. The preservative should allow the red cells to survive after transfusion and to retain the ability to release oxygen into the tissues. Two substances in the red cell are important in oxygen release: adenosine triphosphate (ATP) which regulates red cell viability and 2,3-diphosphoglycerate (2,3-DPG) which determines oxygen release.[25] Other than freezing, there are only two practical red cell preservatives used at this time; one is the ACD solution developed in the early 1940's (during World War II) by Drs. Ross and Finch,[26] and the newer citrate phosphate dextrose (CPD) solution which is associated with a tendency of platelets to clump.

ATP, concerned with viability of red cells, appears to be about the same for both preservatives (Figure 2). The level of 2,3-DPG concerned with oxygen release, however, remains in greater concentration for a longer period with CPD. Consequently, the oxygen delivering capacity is much higher with CPD. The importance of this illustration relates to the requirements of patients. If a patient requires blood with a high immediate oxygen-carrying capacity, it should probably not be more than a week old if stored in ACD solution or two weeks in CPD solution.

It is interesting that the release capacity of transfused cells will return to normal within a day or so after transfusion. Therefore, the use of blood that has been stored for longer periods is probably harmful only when given in large amounts over a short period.[25]

There are many difficulties for transfusion services in provision for blood requirements today. There is great demand for these products and, if we continue to use whole blood for patients who could equally well be treated with components, there simply will not be enough blood

TABLE 3.—*Packed Red Cell Transfusions*

	1972 (Percent)	*1974 (Percent)*
Single unit	25	84
Double unit	33	93
Triple unit	33	84
Four or more*	28	52
All transfusions	30	60

*Includes open heart cases.

TABLE 4.—*Advantages of Packed Red Blood Cells*

- Per unit volume transfused, hemoglobin replacement with packed red blood cells is twice that with whole blood.
- Decreased likelihood of circulatory overload.
- Decreased incidence of nonhemolytic transfusion reactions.
- (?) Decreased incidence of serum hepatitis.
- Safe use of common bloods—O and A in place of B and AB.
- Bonuses:
  - Platelets
  - Leukocytes
  - Cryoprecipitate
  - Factor VIII—depleted fresh frozen plasma
  - Remaining plasma for fractionation into albumin and gamma globulin

TABLE 5.—*Indications for Red Cell Therapy*

Packed red blood cells (80 percent to 90 percent of *all* transfusions)
- Moderate blood loss.
- Chronic anemia not likely to respond to medical therapy.

Whole bank blood
- Moderate to massive blood loss equaling one-half to one times total blood volume; should be alternated with fresh whole blood when loss exceeds total blood volume.
- Exchange transfusion.
- Open heart surgical operation.
- Burns accompanied by anemia and hypoproteinemia.

Fresh whole blood (within 24 hours of collection)
- Probably no good indication if specific components are available.

Frozen blood
- Rare blood types (specific antibody to "public" antigen).
- Patient with multiple red blood cell antibodies.
- Candidates for organ transplantation, (not always helpful since graft survival is sometimes better in patients having received whole blood transfusions).[30]
- Blood shortages.
- Autotransfusion.
- Paroxysmal nocturnal hemoglobinurea.

Packed red blood cells—buffy coat poor
- Patient with severe transfusion reactions due to platelet, leukocyte, or plasma protein antibodies.

Washed red blood cells
- Paroxysmal nocturnal hemoglobinurea.

to go around. There is little justifiable reason today to transfuse a patient with whole blood to improve oxygen-carrying capacity. Packed cells are safer and allow processing of the unused plasma for other products. There is authoritative agreement that 80 percent to 100 percent of transfusions for increasing oxygen capacity should be in the form of packed cells.[27,28] The use of packed cells can be improved through increased staff interest and cooperation. The use of packed cells in the community hospital previously mentioned increased from 30 percent of transfusions to 60 percent between 1972 and 1974 as indicated in Table 3. Since 1974 the staff has mandated that all transfusion units for routine use be given as packed cells. The advantages of using packed red blood cells are indicated in Table 4.[26]

Indications for red blood cell therapy are listed in Table 5.[29] The various components resulting from the separation depicted in Figure 1 are listed with major complications in Table 6.[31] Indications for various components are listed with the alternatives in Table 7.[31]

When a transfusion reaction is thought to have occurred, the transfusion should be stopped immediately. The reaction must be investigated in an organized manner as indicated in Table 8.[10]

How can we, as individual physicians, improve usage of blood? This can be done by (1) justification of blood use, (2) use of appropriate component, (3) use of a transfusion sheet for the medical record (requiring justification by a physician) and (4) encouragement of and participation in an active transfusion committee.

TABLE 6.—*Blood Components and Complications*

Material	*Content*	*Major Complications*
Whole blood	One unit=450-500 ml.	Hepatitis, fever, chills, allergic reactions, circulatory overload, rare hemolytic reactions and malaria.
Red blood cells	One unit=250-300 ml. (yield from one unit of whole blood)	Same as for whole blood but with reduced risk of circulatory overload.
Washed	Same	Same as for RBC but fewer toxic and allergic reactions and probably less risk of hepatitis.
Frozen	Same	Same as for RBC but probably less risk of hepatitis and reduced reactions from leukocytes and platelets.
Platelet-rich plasma	One unit=200-250 ml. (yield from one unit of whole blood)	Hepatitis, fever, chills, allergic reactions, circulatory overload, development of antiplatelet antibodies.
Platelet concentrate	One unit=10-30 ml. (yield from one unit of platelet-rich plasma)	Same as for platelet-rich plasma except no circulatory overload.
Granulocyte rich plasma or concentrate	Granulocytes from 10 units of normal whole blood	Hepatitis, fever, chills, allergic reactions.
Plasma, single donor, (fresh, fresh-frozen, or aged)	One unit=200-250 ml. (yield from one unit of whole blood)	Hepatitis, fever, chills, allergic reactions.
Antihemophilic factor, single donor	100 Factor VIII units in 25 ml.	Hepatitis, fever, chills, allergic reactions, hemolysis due to isoagglutinins.
Antihemophilic factor, multiple donor	250 Factor VIII units in 25 ml.	Same as in AHF.
Hemofil	750 Factor VIII units per 25 ml.	Same as AHF.
Factor IV complex	500 Factor IV units per vial	Hemolysis due to isoagglutinins, very high risk of hepatitis, fibrinolysis (low risk).
Fibrinogen	1 or 2 grams per vial	Hemolysis due to isoagglutinins, hepatitis, fibrinolysis
Albumin	5 grams per dl in 250 and 500 ml 25 grams per dl in 20, 50, 100 ml	Rare
Plasma protein fraction	5 grams per dl in 50, 100, 250 and 500 ml	Rare
Immune serum globulin	16 grams per dl in 2 and 10 ml	Rare
Rh_o (d) immune globulin	1-1.5 ml per vial	Rare

AHF=antihemophilic factor RBC=red blood cells

TABLE 7.—*Indications for Blood Products*

Indications	*First Choice*	*Alternatives*
Severe anemia with hypovolemia (acute hemorrhage)	Whole blood	Red cells plus a plasma expander
Severe anemia without hypovolemia	Red cells	Washed frozen red cells if high risk of allergic reaction
Severe anemia with hypervolemia or diminished cardiac reserve	Red cells; plasma-phoresis if necessary	Same
Severe thrombocytopenia	Platelet concentrate	Platelet-rich plasma
Granulocytopenia with sepsis	Granulocyte-rich plasma	Buffy coat fraction from normal donor blood
Coagulation defects:		
Hemophila (factor VIII deficiency) with severe anemia	Red cells with AHF	Fresh, whole blood with AHF or fresh-frozen plasma
Hemophilia without severe anemia	AHF	Fresh-frozen plasma
Parahemophilia (factor V deficiency) without severe anemia	Fresh-frozen plasma	Fresh plasma
Parahemophilia with severe anemia	Fresh whole blood	Red cells and fresh-frozen plasma
Factor II, VII, IX, or X deficiency without severe anemia	Fresh-frozen plasma	Any preparation of plasma
Congenital factor II, VII, IX, or X deficiency with severe anemia	Red cells, plus either plasma or factor IX complex	Fresh whole blood
Congenital hypofibrinogenemia	Fibrinogen (only when bleeding occurs)	None
Low serum albumin	25 percent salt-poor albumin may be moderately effective	None
Low serum globulin; exposure to hepatitis A	Immune serum globulin	None
Prevention of Rh immunization	Rh_o (D) immune globulin	None

AHF = antihemophilic factor

TABLE 8.—*Investigation of Transfusion Reactions*

Specimens needed
- A. Pretransfusion blood of recipient.
- B. Post-transfusion blood of recipient.
- C. Pilot samples of donor blood
- D. Blood from container implicated in reaction.
- E. Posttransfusion urine.

Investigation procedures (letters refer to specimens listed above)

Immediate
- Examine for visible hemolysis (A,B,E)
- Repeat ABO (A,B,C,D)
- Repeat Rh (A,B,C,D)
- Direct antiglobulin test (A,B)
- Check cross match report and identification of donor and patient

Definitive
- Repeat major and minor cross match (A,B,C)
- Repeat antibody screening (A,B,C)
- Special techniques as necessary
  - Microscopic examination of negatives
  - Prolonged incubation
- Bacteriologic smear and culture (D)

Corroborative
- Identification of any irregular antibody of incompatibility

Optional
- Haptoglobin (A, B)
- Methamalbumin (A, B)
- Bilirubin (B)
- Urea (B)
- Hemosiderin (E)

Dr. Greenwalt,[32] Medical Director of the American Red Cross, has stated that, in the future, "Each donation will serve many patients and whole blood transfusion will be a historical curiosity."

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Appendix

Standards for Blood Banks and Transfusion Services

I. General Policies and Definitions

A. All phases of the selection of blood donors and of the collection, storage, processing, and transfusion of blood shall be the responsibility of a qualified, licensed physician with a thorough knowledge of blood bank methods and of transfusion principles and practices.

B. There shall be an adequate staff to carry out the various phases of a blood transfusion service under his supervision.

C. Suitable quarters and equipment shall be available to maintain safe and acceptable standards.

II. Donors and Donor Blood

A. Criteria for donor selection:
These shall be applied on the day of donation by suitably trained persons and the results shall be appropriately recorded.

1. It shall be determined that the blood donation will not be detrimental to the donor. The following minimum requirements shall apply:

a. Prospective donors with a history of chronic diseases of the heart, kidneys, lungs, liver and so forth, or with a history of cancer, of abnormal bleeding tendencies or of convulsions after infancy shall be excluded subject to evaluation by a qualified physician on the day of donation.

b. Except for reasonable qualifying circumstances, the interval between individual donations should be at least eight weeks.

2. The donor shall be free of disease transmittable by blood transfusion as ascertained at the time of collection in accordance with the guide for donor requirements.

3. A guide for donor requirements

a. General appearance
The donor shall appear to be in good health and free from acute respiratory diseases.

b. Age
Blood donors shall be between the ages of 17 and 65 (up to 66th birthday) with the following exceptions:

(1) Donors between ages of 17 and 21 must have a written consent signed by a parent or guardian, unless local law defines the legal age for blood donation as 18. Since laws defining minors vary from state to state, particularly relating to those who are married or on active duty in the federal armed services, legal opinion should be obtained.

(2) After the 66th birthday, donors may be accepted at the discretion of the blood bank physician if they have specific written consent from a physician within two weeks before the date of donation provided they meet all other criteria for acceptability.

c. Temperature
The oral temperature shall not exceed 37.5° C (99.6° F).

d. Hemoglobin or hematocrit
The preferred method is determination of the hemoglobin concentration.

(1) The hemoglobin level shall be no less than 12.5 grams per dl for female donors, and no less than 13.5 grams per dl for male donors.